REMARKS

Claims 64-83 are pending. In the office action dated January 21, 2003, the Examiner rejected claims 64-83 under 35 U.S.C. § 112, paragraphs one and two, and objected to the specification because of informalities (the inclusion of a graph in the specification). The Examiner also concluded that the pending claims were free of the art of record because "the prior art fails to teach or suggest the use of such contrast agents in the methods of MRI and interventional therapy as claimed."

Applicants have herein amended the specification to delete the graph from page 31 and to replace it as a drawing (Figure 1). Applicants have amended the specification to conform to these changes, including the addition of a "Brief Description of the Drawings" at page 9 to describe the drawing. For clarity, Applicants have also included substitute pages 9 and 31 herein. No new matter has been added. Applicants have also herein amended claims 64-65, 67, and 71-83, cancelled claims 66 and 68-70, and added claim 84. Support for the amendments may be found throughout the specification, including, e.g., at pages 28-29, 37, and 39-42. Accordingly, claims 64-65, 67, and 71-84 are pending.

Applicants respectfully request reconsideration and allowance of claims 64-65, 67, and 71-84.

Request for Initialed PTO Form 1449

Applicants note that they have not received initialed copies of the PTO form 1449 (2 pages) filed on April 12, 2002. Applicants respectfully request initialed copies in the next communication indicating the Examiner has considered the references cited therein. Duplicate copies of the PTO form 1449 are attached hereto.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 64-82 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner stated:

> The claims fail to describe the SDTBM using reasonably generic terminology to convey that applicant had possession of such generic terminology as described in the specification. For example, the claims define the SDTBM to be a moiety that 'comprises one or more alkyl, cycloalkyl, aryl, or heterocyclo groups or combinations thereof' in claim 64. This definition would encompass almost any organic moiety and a vast and diverse group of biomolecules and small organics . . . . [T]he generic terminology in the claims does not describe the association between these moieties in combination, i.e., how are an alkyl and aryl structurally related, etc., or because of the open terminology "comprises" it is unclear as to what other moieties may be present . . . . The specification clearly does not reasonably convey that any possible organic molecule can be attached to the chelate to provide the specific functionality set forth for the contrast agent in the claim (e.g., the R1 value and the percent binding). In fact, the specification only reasonably conveys the use of a limited number of specific small molecule groups as the SDTBM."
>
> See Office action dated 1/21/03, pages 2-3.

Applicants respectfully disagree. Pending independent claim 64, and dependent claims 65, 67, and 71-83, are directed to a method for monitoring treatment of a tissue comprising HSA. As amended, the method includes administering a contrast agent to a patient. The contrast agent comprises an organic chelating agent complexed to a paramagnetic metal ion, where the organic chelating agent is selected from the group consisting of DTPA, DOTA, DTPA-BMA, and HP-DO3A, and where the organic chelating agent is covalently bound to a structure : $-(L)_m$-SDTBM either at a methyl carbon of an acetate chelating moiety of the organic chelating agent or at an ethylene carbon backbone moiety of the organic chelating agent. In addition, claim 64 recites that the SDTBM comprises zero to six linear or branched alkyl groups having 1 to 10 carbon atoms; zero to five cycloalkyl groups; or zero to five aryl groups; or combinations thereof, where the alkyl, cycloalkyl, or aryl groups can be optionally and independently substituted with from 1 to 5 ether, carboxylate, or sulfate moieties. Finally, claim 64 recites that the contrast agent must further have:

1) an R1 observed value in a 4.5 wt% solution of HSA at 25 °C of greater than about 10 mM^{-1} sec^{-1}; and

2) a percent binding to HSA in a 4.5 wt%, pH 7.4 solution of HSA of greater than about 10%.

Applicants respectfully assert that the specification provides adequate written description under 35 U.S.C. § 112, first paragraph for the method of MR imaging recited in the pending claims. First, Applicants describe general physical, structural, and functional features of the claimed contrast agents on pages 19-28 of the specification. For example, Applicants note that the contrast agent should include physical and structural features (e.g, hydrophobicity; rigid non-planar groups) that promote the contrast agent's ability to bind reversibly to HSA and to demonstrate relaxivity increases upon binding. In addition, Applicants set forth numerous examples of the claimed contrast agents (e.g., greater than 20 examples) demonstrating such features on pages 39-42 of the specification.

Secondly, the pending claims include a structure of the MR contrast agent to indicate both how and where the IEM metal chelate is covalently bound to the -$(L)_m$-SDTBM structure – either at a methyl carbon of an acetate chelating moiety of the organic chelating agent or at an ethylene carbon backbone moiety of the organic chelating agent. The pending claims also recite structure for the organic chelating agents and set forth representative paramagnetic metal ions. The various structures on pages 36-37 and 39-42 provide written description for such language.

Third, the pending claims recite that the SDTBM comprise zero to six linear or branched alkyl groups having 1 to 10 carbon atoms; zero to five cycloalkyl groups; or zero to five aryl groups; or combinations thereof, where the alkyl, cycloalkyl, or aryl groups can be optionally and independently substituted with from 1 to 5 ether, carboxylate, or sulfate moieties. Applicants' specification provides adequate written description for this genus. For example, Applicants have provided a representative synthetic scheme at pages 50-57. Applicants have set forth more than 20 specific examples of contrast agents on pages 39-42. Importantly, Applicants' examples include widely diverse structural arrangements of alkyl, cycloalkyl, and aryl groups, many of which are substituted with moieties including ether, carboxylate, and sulfate groups at a diverse range of positions. Thus, both Applicants' general description and their particular examples provide written description for the genus of SDTBMs claimed.

Applicants also point out that the pending claims set forth physical and/or functional requirements for the MR contrast agent for use in the recited method. For example, the contrast

agent must demonstrate an R1 observed value in a 4.5 wt% solution of HSA at 25 °C of greater than about 10 mM^{-1} sec^{-1}. In addition, the contrast agent must exhibit a percent binding to HSA in a 4.5 wt%, pH 7.4 solution of HSA of greater than about 10%. Assays to determine these physical and functional requirements are disclosed in the specification. For example, at page 27, Applicants describe that the extent of binding to HSA can be measured by a variety of equilibrium binding methods, including equilibrium dialysis or ultrafiltration. At pages 28-29, Applicants set forth a method for determining relaxivity of a contrast agent in the absence and presence of a desired protein target, e.g., HSA. Examples 1-3 demonstrate R1 measurements and HSA binding experiments. Therefore, not only does the specification provide adequate written description for the structures of the SDTBMs and contrast agents of the pending claims, it also provides written description for the physical properties of the contrast agents (e.g., binding to HSA target; R1 values). Moreover, the specification discloses that the claimed structure of the contrast agent and its physical property of HSA protein binding are correlated with an increase in relaxivity of the MR contrast agent upon binding to HSA. Thus, Applicants have disclosed a correlation between structure and function; see, e.g., pages 19-22; 28-29; 32-33; and Examples 1-3. In sum, the breadth of structural arrangements of the SDTBM moieties as evidenced in the species disclosed on pages 39-42, in combination with the claimed physical and functional characteristics of the resulting contrast agent, supports the breadth of the genus of SDTBMs (and contrast agents) claimed. Applicants respectfully suggest that all of the evidence outlined above demonstrates that Applicants had "possession" of the invention as claimed.

As one last point, Applicants note that the Federal Circuit has recently discussed the "possession" inquiry with respect to the written description requirement of 35 U.S.C. § 112. See Enzo Biochem., Inc. v. Gen-Probe Inc., 296 F.3d 1316, 1330 (Fed. Cir. 2002) (noting that "[a]pplication of the written description requirement is not subsumed by the 'possession' inquiry. A showing of 'possession' is ancillary to the *statutory* mandate that '[t]he specification shall contain a written description of the invention'") (emphasis in the original). Duplicate copies of the Enzo decision are included herewith for the Examiner's reference. In fact, the court in Enzo referred to the PTO's own Written Description Guidelines when it held that the written description requirement is satisfied by a patentee's disclosure of relevant structural and physical characteristics, e.g., "by complete or partial structure, other physical and/or chemical properties,

functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Enzo, 296 F.3d at 1324.

Given all of the above, Applicants respectfully suggest that the specification provides adequate written description of the SDTBMs and contrast agents of the invention, including the types and relative positioning of chemical moieties making up the SDTBM and contrast agents. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, first paragraph – New Matter Rejection

The Examiner also rejected claim 82 as including new matter. In particular, the Examiner stated that the specification did not include phosphodiester or amide moieties as the linker L, as claimed in claim 82. Applicants respectfully disagree. On page 29 of the specification, Applicants note that "[e]xtended blood half-life may be achieved by including a linking group (L) which functions as a blood half-life extending moiety ("BHEM") to reduce the rate of hepatocyte uptake of the contrast agent. The present specification then sets forth phosphate diester moieties as one example of a BHEM; see page 30, line 16. The present specification also sets forth a structure having an amide BHEM at page 39, the bottom structure. Accordingly, Applicants respectfully assert that claim 82 does not include new matter and respectfully request the withdrawal of the new matter rejection.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 64-83 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner rejected claims 64-83 as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. In particular, the Examiner stated that:

> The omitted structural cooperative relationships are: the structural relationship between the various chemical moieties recited therein. The claims recite that the SDTBM "comprises" various organic moieties; however, this recitation omits any structural relationship to each other (e.g., when in combination thereof) or to other possible chemical moieties which are encompassed by the open terminology

"comprising." It is improper to define a specific chemical compound, such as the SDTBM by only listing chemical moieties (or parts) which it comprises, since this fails to define what else may be present and because structural relationships of chemical moieties to form compounds is so diverse. Further complicating the definition of SDTBM is its differentiation to the chelate molecule.

See Office Action dated 1/21/03, pages 3-4.

Applicants respectfully disagree. As amended, present claim 64 recites the administration of a contrast agent comprising a physiologically compatible organic chelating agent complexed to a paramagnetic metal ion. The organic chelating agent can be selected from the group consisting of DTPA, DOTA, DTPA-BMA, and HP-DO3A. The organic chelating agent is covalently bound to a structure : $-(L)_m$-SDTBM either at a methyl carbon of an acetate chelating moiety of the organic chelating agent or at an ethylene carbon backbone moiety of the organic chelating agent. In addition, claim 64 recites that the SDTBM comprises zero to six linear or branched alkyl groups having 1 to 10 carbon atoms; zero to five cycloalkyl groups; or zero to five aryl groups; or combinations thereof, where the alkyl, cycloalkyl, or aryl groups can be optionally and independently substituted with from 1 to 5 ether, carboxylate, or sulfate moieties.

Applicants respectfully assert that the pending claims do not omit essential structural cooperative relationships of elements. First, Applicants note that the pending claims include a structure of the MR contrast agent to indicate both how and where the IEM organic chelating agent is covalently bound to the $-(L)_m$-SDTBM structure – either at a methyl carbon of an acetate chelating moiety or at an ethylene carbon backbone moiety. (See also, e.g., structures on pages 36-37 and 39-42). Thus, the differentiation of the SDTBM to the chelate molecule is defined in the present claims. The pending claims also recite structure for the organic chelating agents and set forth representative paramagnetic metal ions.

In addition, the pending claims recite that the SDTBM comprise zero to six linear or branched alkyl groups having 1 to 10 carbon atoms; zero to five cycloalkyl groups; or zero to five aryl groups; or combinations thereof, where the alkyl, cycloalkyl, or aryl groups can be optionally and independently substituted with from 1 to 5 ether, carboxylate, or sulfate moieties. With regard to the Examiner's comment that "[i]t is improper to define a specific chemical

compound . . . by only listing chemical moieties which it comprises, since this fails to define what else may be present," Applicants respectfully note that the open claim language "comprising" *necessarily* fails to define "what else may be present" and how it may be structurally arranged relative to any moieties explicitly defined in the claim. In addition, Applicants note that they have set forth more than 20 examples of contrast agents on pages 39-42. Importantly, Applicants' examples define a genus that includes widely diverse structural arrangements of alkyl, cycloalkyl, and aryl groups, many of which are substituted with moieties including ether, carboxylate, and sulfate groups at a diverse range of positions. Applicants respectfully assert that to limit them to closed language such as "consisting of" or to their explicit species as set forth in claim 83 would improperly limit the breadth of the genus that Applicants have enabled, described, and defined. Accordingly, Applicants respectfully suggest that the pending claims are not indefinite, and respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Objection to the Specification

The Examiner objected to the specification because of the inclusion of a graph on page 31. Applicants have herein amended the specification to remove the graph and to replace it as a drawing (Figure 1). Applicants have amended the specification to conform to this change, including the addition of a "Brief Description of the Drawings" section. No new matter has been added. Substitute specification pages are also included herewith. Accordingly, Applicants respectfully request withdrawal of the objection to the specification.

CONCLUSION

In light of all of the above, Applicants respectfully request reconsideration and allowance of all claims. The Examiner is invited to call the above-referenced attorney if doing so would expedite prosecution.